REMARKS

On December 16, 2008, Applicants filed a Notice of Appeal in this Application. At this time, Applicants are filing a Request for Continued Examination to withdraw the appeal and continue the examination of the application.

Claims 1, 2, 5, 6, 8, 9 and 11-24 are currently pending in this application. Claims 11-24 stand withdrawn. Claims 3, 4, 7 and 10 were previously canceled. Claims 1, 2, 5, 6, 8 and 9 are now under continued examination and stand finally rejected.

Claims 1, 2, 5, 6, 8 and 9 have been amended without prejudice to filing a continuing application claiming any deleted subject matter. Support for the amendments is found in the application as originally filed. No new matter has been added.

35 U.S.C. § 112, 2nd Paragraph Rejections

In the Office Action of June 20, 2008, the Office rejected claims 1-2, 5-6, and 8-9 under § 112, 2nd Paragraph as being indefinite. Specifically, the Office asserted that the claims are not clear as to the patient population being administered the treatment in the administering step. In the reply of December 2, 2008, Applicants responded by amending the rejected claims. However, in the Advisory Action of January 14, 2009, the Office indicated that the amendments were not entered, because they raise new issues that would require further consideration.

In order to enter the amendments, Applicants submit with this response a Request for Continued Examination. In this response, while not agreeing with the Office's assertion and solely to move prosecution forward, Applicants have again amended the rejected claims to more explicitly recite the patient population to be treated by the method. Specifically, Applicants have added to claims 1-2 and 5-6 the limitation "to a human having androgen-dependent prostate cancer," and have added to claims 8-9 the limitation "to a human who has had or presently has androgen-dependent prostate cancer." With these added limitations, Applicants have fully responded to the Office's concerns expressed in the Office Action of June 20, 2008, and respectfully request the withdrawal of these rejections.

35 U.S.C. § 112, 1st Paragraph Rejections

In the Office Action of June 20, 2008, the Office rejected claims 1-2, 5-6, and 8-9 under § 112, 1st Paragraph for lack of enablement. Specifically, the Office alleged that the claims are not enabled to the extent that they read on the prevention of prostate cancer in a patient not having prostate cancer. In the reply of December 2, 2008, Applicants responded by amending the rejected claims. However, in the Advisory Action of January 14, 2009, the Office indicated that the amendments were not entered, because they raise new issues that would require further consideration.

In order to enter the amendments, Applicants submit with this response a Request for Continued Examination. In this response, while not agreeing with the Office's assertion and solely to move prosecution forward, Applicants have again amended the rejected claims to limit the patient population to be treated by the method. Specifically, Applicants have added to claims 1-2 and 5-6 the limitation "to a human having androgen-dependent prostate cancer," and have added to claims 8-9 the limitation "to a human who has had or presently has androgen-dependent prostate cancer." With these added limitations, Applicants have fully responded to the Office's concerns, and respectfully request the withdrawal of these rejections.

35 U.S.C. § 103(a) Rejections

In the Office Action of June 20, 2008, the Office rejected claims 1, 2, 5 and 6 under 35 U.S.C. § 103(a) as being unpatentably obvious over Gunawardena et al. (The Prostate, 2000, vol. 44, pages 287-295) in view of Sheu et al. (Life Sciences, 1999, vol. 65, pages 197-206). The Office alleged that Gunawardena et al. disclose that antioxidants have been associated with a reduced risk of cancer in various tissues, including the prostate, and that α–tocopherol and other antioxidants inhibit the growth of human prostate cancer cells through apoptosis.

The Office further alleged that Sheu et al. compare the activities of α–tocopherol and PMCol on platelet aggregation and antioxidant activity, and that PMCol was shown to have greater antioxidant activity than α–tocopherol. Thus, the Office asserted, it would have been *prima facie* obvious to one of ordinary skill in the art to administer PMCol to patients having androgen-dependent prostate cancer, especially given the correlation between anti-oxidant activity and inhibition of prostate cancer cell growth as taught in Gunawardena et al. The Office further asserted that the skilled artisan would have been highly motivated to administer the instantly claimed PMCol

to prostate cancer patients, based on the reasonable expectation that structurally similar species usually have the same properties.

In the reply of December 2, 2009, Applicants presented arguments and submitted a supporting reference (Koga, et al., *Lipids* 33 (1998) 589-595) to overcome the Office's alleged *prima facie* obviousness finding. In the Advisory Action of January 14, 2009, the Office entered Koga et al. into the record, but indicated that it was not persuaded by Applicants' arguments, both for reasons of record and additionally because numerous compounds that inhibit prostate cancer cell proliferation do not contain a phytyl tail.

In this response, while not agreeing with the Office's assertion and solely to move prosecution forward, Applicants have amended the rejected claims to recite that the compound used in the claimed method "specifically binds androgen receptor." Because this limitation is not taught or suggested in the documents cited against the claims, the claims cannot be unpatentably obvious over the cited documents. In addition, in the Advisory Action of January 14, 2009, the Office mischaracterized Applicants' arguments and did not respond to Applicants' arguments and accompanying evidence from the literature showing (1) that PMCol and α–tocopherol have very different properties based on structural differences that are relevant to the invention, and (2) that antioxidant activity does not necessarily suggest that a compound will be effective against a specific form of cancer. Accordingly, Applicants respectfully request that the Office reconsider and withdraw the obviousness rejections.

1. The Cited Documents Do Not Teach or Suggest Androgen Receptor Binding

In the specification, Applicants clearly establish that the claimed methods of treating androgen-dependent prostate cancer work by the administered compound binding to androgen receptor and acting as an androgen receptor antagonist. See, e.g., paragraphs [0013], [0018], [0035], [0050], [0052] - [0054], [0093], [0109], [0115], and [0122]. In addition, to prevent penetration of the blood-brain barrier and thus to limit anti-androgen activity to the targeted peripheral organs, the compounds administered in the claimed method are preferably water soluble, in sharp contrast to α–tocopherol, which is practically insoluble in water. See paragraph [0035]. Finally, the compounds administered in the claimed method are pure androgen receptor antagonists that do not exhibit even partial agonist activity. See paragraph [0035]. Applicants show throughout the specification that the efficacy of the claimed method is related to the ability of the administered compounds to bind to androgen receptors, not to any anti-oxidant properties that the compounds

may possess. Throughout the examples, the activity of PMCol is compared not to other known anti-oxidants, but to bicalutamide, a non anti-oxidant androgen receptor antagonist.

As amended, the pending claims now recite the binding of the administered compound to androgen receptor. Neither Sheu et al. nor Gunawardena et al. suggest this claim limitation. Gunawardena et al. teach that antioxidants modulate human prostate cancer cell proliferation by affecting cell growth cycles leading to apoptosis. Abstract, p. 290, p. 293. Increased apoptosis decreases proliferation of dividing cells. Gunawardena et al. do not teach that antioxidants bind to androgen receptor. Similarly, Sheu et al. does not in any way suggest that PMCol could bind to androgen receptor. Instead it allegedly discloses PMCol's anti-oxidant activity in the context of standard platelet aggregation, lipid peroxidation, and free radical scavenging assays. These assays are irrelevant to androgen receptor binding activity.

In light of Applicants' amendments to the claims reciting that the compound used in the claimed methods bind androgen receptor, the combined references do not teach all of the limitations of the amended claims. Accordingly, Applicants respectfully request that the Office reconsider and withdraw the obviousness rejections of claims 1, 2, 5, and 6.

2. The Office Did Not Fully Consider Relevant Structural Differences

The cited references and other art of record show that that PMCol and α–tocopherol have substantially different functional properties, and a presumption of obviousness based on structural similarity is overcome where there is no reasonable expectation of similar properties. MPEP 2144.09 (V).

The two structures are shown on page 15 of the Office Action of June 20. As noted by Applicants in paragraph [0096] of the specification, α–tocopherol has two main components: the chromanol moiety and a sixteen carbon phytyl tail. In PMCol, on the other hand, a single carbon methyl group is substituted for the sixteen carbon phytyl tail. This structural difference leads to significant functional differences between the two structures, because PMCol is water soluble and α–tocopherol is highly lipophilic with limited water solubility. Biologically, the phytyl tail (absent in PMCol) increases the lipophilicity of α–tocopherol and contributes to its tissue and subcellular distribution mostly in the cellular membranes and adipose tissue, which is very different from that of a more water soluble PMCol that resides mostly in the cytoplasm and nuclei, the major sites of localization of hormone receptors and cellular signaling molecules. See specification, paragraph [0096]. In addition, unlike α–tocopherol, because PMCol is water soluble, it will not cross the

blood brain barrier, and so will not affect brain androgen receptors. See specification, paragraph [0035].

Thus, the two compounds act very differently in biological systems, and the Office appears to acknowledges this difference in the Office Action of June 20, 2008 (PMCol is more hydrophilic than α–tocopherol, as taught by Sheu et al.). But this difference removes any expectation of similar properties due to the shared Chromanol moiety. For example, consider Burton and Traber (Ann. Rev. Nutr. 1990, 10: 357-382), a non-patent publication of record submitted to the Office with the Information Disclosure Statement of October 4, 2004. This review emphasizes the importance of α–tocopherol for protecting the integrity of lipid structures in vivo, especially membranes. See p. 360, second full paragraph. Burton and Traber note that although the chroman group is responsible for the antioxidant activity of the α–tocopherol molecule, the phytyl group, which is absent from PMCol, largely determines the kinetics of transport to and retention within membranes. Page 361. Because α–tocopherol functions largely within membranes to protect them from oxidation, this structural difference is fundamental to the anti-oxidant function of the molecule.

This is clearly demonstrated by Koga, et al. (Lipids 33 (1998) 589-595), which was entered into the record with the January 14, 2009 Advisory Action. Koga et al. compared the protective effect of α–tocopherol, PMCol, and PCh (an α–tocopherol analog with a phosphorolated but still elongated phytyl-like group) against oxidative hemolysis of human erythrocytes. In contrast to the other two compounds, PMCol provided no protection in oxidized erythrocyte suspensions, and during preincubation, PMCol was incorporated into cells at only one-third to one-fourth the concentration of the other two compounds. See abstract. Koga et al. note that although the three structures are identical except for the substituents at the 2-position (where α–tocopherol has a phytyl chain and PMCol has a methyl group), their antioxidant effects are much different from one another in a heterogeneous system (i.e. in cells) "because of their inherent physical properties." Page 593, column 1, last full paragraph. The phytyl chain acts as an anchor to retain the chromanol moiety within membranes, and unlike PMCol, α–tocopherol is well incorporated into cultured cells because of the high affinity of its phytyl group for cell membranes. See p. 593, column 2, first and second full paragraphs. All of this was known by skilled artisans at the time of the invention.

Gunawardena, et al. show that α–tocopherol and two other anti-oxidants not containing chromanol groups can inhibit prostate cancer cells through apoptosis, and α–tocopherol worked only with androgen responsive prostate cancer cell lines. Gunawardena, et al. do not teach or suggest using any molecule containing a chromanol moiety for prostate cancer treatment other than

α–tocopherol. Certainly, a skilled artisan at the time of the invention, knowing that the phytyl chain of α–tocopherol helps to incorporate the molecule into cells, would not have been motivated by Gunawardena to substitute PMCol for α–tocopherol. Indeed, the skilled artisan would not have expected PMCol to work at all, because it lacks a phytyl chain and thus would not be incorporated into the cell membrane to carry out its anti-oxidant function. Because the skilled artisan would not have had a reasonable expectation of success in practicing the claimed method, the claimed method can not be obvious. See MPEP 2143.02.

In addition, Sheu at al. do not provide a motivation to combine the references to produce the method of the present invention. Sheu et al. teach that PMCol is an anti-oxidant that can (1) inhibit human platelet aggregation, (2) inhibit lipid peroxidation in rat brain homogenates, and (3) scavenge the stable free radical DPPH. However, none of these effects is at all analogous to the treatment of prostate cancer within cells. Indeed, a close reading of Sheu et al. reveals that all of these results occurred within an extracellular aqueous solution, either outside of or on the outer surface of any cells present. In such cases, PMCol would not have to penetrate or incorporate itself into the lipid bilayer of the cell membrane, and the phytyl chain would have less functional importance (and may even be a disadvantage).

For example, Sheu at al. teach that the outer membrane has a dominant role in platelet aggregation, and that PMCol works in a way that displaces fluorescent tags on the outer platelet membrane. Thus, PMCol apparently does not have to penetrate the cell to inhibit platelet aggregation. See page 204. In addition, the rat homogenates in which lipid peroxidation was measured are cell free, aqueous systems. Sheu at al. propose that the high activity shown by PMCol in this assay was partly the result of having a methyl group rather than a phytyl chain, because methyl more readily associates with homogenized brain tissue membrane. See page 205. Finally, the scavenger assay also occurred with free molecules in an aqueous solution, not at all analogous to treating cancer within a cell, where the phytyl chain of the α–tocopherol group would allow for cell penetration and the methyl group of PMCol would not. Clearly, Sheu et al. provide no motivation for the skilled artisan to use PMCol in treating prostate cancer, and given the structural and functional differences between α–tocopherol and PMCol, a skilled artisan would not have expected success in trying such a substitution in the treatment taught by Gunawardena.

In the Advisory Action of January 14, 2009, the Office dismisses the structural differences explained above, stating that the skilled artisan would be motivated by structural similarity and that "numerous compounds that inhibit prostate cancer cell proliferation do not contain a phytyl tail."

This mischaracterizes Applicants' argument. Applicants are not arguing that a phytyl tail is necessary for anticancer activity, but rather that the hydrophilic properties of PMCol as compared to the hydrophobic properties of α–tocopherol (caused in part by the phytyl tail) would lead to substantially different biological activity between the compounds, such that the skilled artisan would not be motivated to simply substitute one for the other. Because the two compounds have such biologically significant functional differences, there is no presumption of obviousness based on structural similarity. Accordingly, Applicants respectfully request that the Office reconsider and withdraw the obviousness rejections.

3. Antioxidant Activity and Cancer Treatment

The Office argues that the teaching of Sheu et al. that PMCol functions as an effective anti-oxidant in certain in-vitro tests supports the Office's assertion that it would have been obvious for the skilled artisan to use PMCol as a treatment for prostate cancer. This argument misreads the limited teachings of Sheu et al. and greatly overstates any established correlation between anti-oxidant activity and cancer treatment. Sheu et al., the only reference cited in the action that tested PMCol, does not even mention the use of anti-oxidants to treat cancer or oxygen reactive species as a possible cause of cancer. Instead, Sheu et al. state that anti-oxidants show promise in the treatment of atherosclerosis and that oxygen reactive species may cause aging, neuron degeneration, and liver disease, in addition to atherosclerosis. See page 198. There is no teaching or suggestion in Sheu et al. that because an agent is found to have anti-oxidant activity, it would therefore be an effective treatment for cancer, let alone specifically for androgen-dependent prostate cancer.

Furthermore, Gunawardena et al. note that although antioxidants have been associated with reduced risk of cancer in various tissues, the anti-oxidant β-carotene has actually been shown to increase prostate cancer risk, and that anti-oxidants vary widely in their effectiveness as treatments for prostate cancer. See pages 291-293. Barrett (non-patent literature of record submitted with the Information Disclosure Statement of March 10, 2008) teaches that vitamin C, a well known anti-oxidant, is not effective as a cancer treatment. Indeed, the vast majority of compounds effective against cancer are not classified as anti-oxidants, and the vast majority of anti-oxidants have not been shown to be effective against prostate cancer. Thus anti-oxidant activity alone is not enough to suggest to the skilled artisan that a given compound would be effective against prostate cancer.

This is particularly true in the case of the present invention, where the compounds administered in the method work by acting as androgen receptor antagonists, not as antioxidants.

The specification emphasizes throughout that the claimed method works against prostate cancer cells mainly because the compounds are effective androgen receptor antagonists. Most known androgen receptor antagonists are not anti-oxidants, and most anti-oxidants do not have PMCol's anti-androgenic activity. Thus, PMCol's known anti-oxidant activity as taught in Sheu et al. provides the skilled artisan no evidence of a likelihood of success in combining the cited references and cannot be used to assert that the method of the present invention was obvious at the time of the invention.

In the Advisory Action of January 14, 2009, the Office dismisses this argument, stating that although "it is certainly true that there are antioxidants that do not function as anticancer agents, this is not pertinent to the present rejection." The Office adds "other antioxidants are not under examination." Yet, the obviousness rejections are based substantially on what the cited references teach about comparative antioxidant activity, including the Office's assertion that "PMC is a more potent antioxidant than α–tocopherol." Thus, contrary to the Office's assertion, the relationship (or non-relationship) between anticancer activity and antioxidant activity is central to the present rejection. Because the combined references considered in light of the other documents of record in the application do not support such a relationship, Applicants respectfully request that the Office reconsider and withdraw the obviousness rejections.

In view of (1) Applicants' amendments reciting the binding of the administered compounds to androgen receptor, (2) the biologically significant structural differences between PMCol and α–tocpherol, and (3) the lack of a connection between the claimed invention and anti-oxidant activity as discussed in the cited references, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections of claims 1, 2, 5, and 6 over Gunawardena et al. and Sheu et al.

Conclusion and Fees

In light of the amendments and arguments presented herein, Applicants respectfully request that the claims rejections be withdrawn and that a Notice of Allowance be issued.

So that the claim amendments will be entered and considered, Applicants submit with this response a Request for Continued Examination. In addition, a Petition for a One Month Extension of Time is also submitted with this response, to make this a timely reply. Please charge the Request for Continued Examination and Extension of Time fees to Deposit Account No. 17-0055. No other fees or time extensions are believed due; however, if an additional extension of time is needed, consider this the required petition, and if additional fees are required, please charge any additional fees in this or any future response to Deposit Account No. 17-0055.

Respectfully submitted,
Todd A Thompson, et. al.

/Keith H. Heidmann/

By: Keith H. Heidmann, Reg. No. 61,774
Charles L. Leeck, Reg. No. 50,343
Attorney for Applicants
QUARLES & BRADY LLP
411 East Wisconsin Avenue
Milwaukee, WI 53202-4497

TEL (414) 277-5753
FAX (414) 978-8762